PERSONALIZED RENAL TRANSPLANTATION: A View from the EU 28+ Countries

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Kidney transplantation is the prototypical example of the routine practice of personalized/individualized therapy. To optimize individual outcomes, donors and recipients are matched on the basis of their HLA genotypes, and histocompatibility is further tested in vitro. The mandatory medical immunosuppression therapy is adjusted based on the results of these tests and the clinical course.

Because full HLA matching occurs only in homozygous twins, and recognizable antigens differ between HLA type mismatches, in silico tools for epitope matching such as the PIRCHE score or the HLAMatchmaker may facilitate a refined risk stratification of the alloresponse (1).

In addition, optimal HLA matching is rarely achieved because other important factors need to be considered in allocation algorithms. For example, in deceased donor transplantation, most patients die with a functioning graft; therefore, some countries such as the United States and Australia have changed their allocation procedures to match the donor organ quality with the expected recipient survival to avoid futility.

Because individual prediction of posttransplantation survival is imprecise, a different allocation strategy exists in most European transplant networks. Of note, several different transplant networks with different allocation algorithms exist in the Europe 28+ region, and the rate of live donor transplantation ranges from more than 90% (Turkey, Iceland) to less than 10% (Croatia, Italy). Therefore, no general comparison is possible. For example, in Eurotransplant, covering eight countries, regular allocation following special programs assigns each single HLA class I (A, B) and class II (DR) match equal "bonus points" equivalent to 2 years of active waitlisting.

A solution to optimize HLA matching also in live donor transplantation would be to include not only HLA or AB0 incompatible pairs into an organ exchange network but also poorly matched younger potential live donor recipients with a likely need for a retransplant after some years.

Since the emergence of a calcineurin inhibitor (CNI)-based immunosuppressive triple regimen as the standard, and owing to disappointing results from interventional studies on humoral alloimmunity, new individualized approaches are needed to further improve outcomes.

New approaches and outlook

Evidence is emerging that non-HLA alloimmunity also plays an important role in long-term graft attrition, and this may explain some of the chronic humoral alloimmune processes in the absence of anti-HLA donor-specific antibodies.

Opelz et al. (2) found in their analysis of over 3000 HLA identical sibling transplants a graded risk of graft loss depending on the degree of overall sensitization against a test panel of healthy volunteers (of note, HLA–DP mismatch was not determined in that study). In addition, it is clinically well known that in patients with Alport syndrome, anticollagen antibodies may develop after transplantation, and few of these patients experience premature graft loss.

Besides the known genetic variability of individuals by roughly 10 million single nucleotide polymorphisms, MacArthur et al. (3) were among the first to show that each individual human has roughly 10 to 20 full loss-of-function mutations. Together with differences of nonsynonymous single nucleotide polymorphisms in the genome, these may contribute to indirect allorecognition (Figure 1).

These examples support the hypothesis that non-HLA alloimmunity has a clinical consequence. The iGeneTrain consortium (4) seeks to elucidate some of these enigmas, and recently Reindl-Schwaighofer et al. (5) showed that in fact non-HLA incompatibilities on a genomewide level contribute to graft loss. This association was observed to be independent of HLA matching and other known risk factors for graft loss. Given the many genomewide individual donor-to-recipient mismatches, it is likely that matching will not be an option, at least in the setting of deceased donor transplantation. Live donors, however, may be included into a paired exchange program if stratification based on genotyping yields many incompatibilities with the recipient and thus a higher risk of graft loss. Certainly, these results and strategies need to be validated and potentially implemented by others.

Another fascinating approach to track the alloimmune response individually became available with the new sequencing technologies. Next-generation sequencing of the highly diverse T cell receptor repertoire allows for tracking of individual alloreactive T cells. Recently an analysis on that topic was published by DeWolf et al. (6). If one may speculate further, it may potentially be possible to determine the epitope's amino acid by the T cell receptor genetic sequence, as has been shown by Dash et al. (7) and Reindl-Schwaighofer et al. (8) in a selected group of infections.

These great areas of scientific progress may allow the transplantation physician in the future to individualize immunosuppressive therapy, not only through level monitoring but also according to sequentially measured alloresponse readouts.

Thus, research into HLA alloimmunity has led to great clinical progress and the development of solid-phase technologies that are now standard in all transplantation centers. Maybe we need to redo this research, also taking non-HLA effects into account. It is exciting to have technologies available that allow further improvement of kidney transplantation research and also ultimately provide better and individual treatment for our patients. ■

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References

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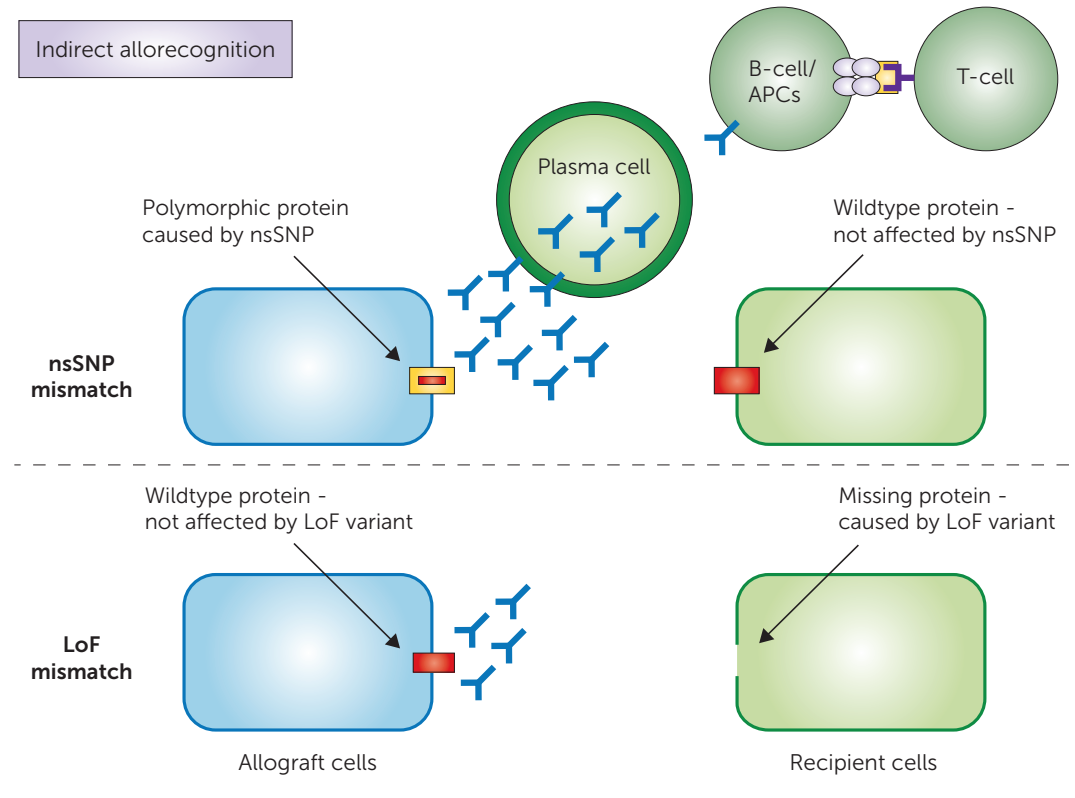
Figure 1. Concept of indirect allorecognition of polymorphic proteins (nonsynonymous SNPs, upper panel) and "loss of function" (homozygous knockout) variant mismatches (lower panel) between donors and recipients



SNP = single nucleotide polymorphism; LoF = loss of function. Reprinted with permission from Reindl-Schwaighofer R, et al. (9).